BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

JANUARY 1940

THE ADRENAL MEDULLA*

W. B. CANNON
Professor of Physiology, Harvard University

A FACT of fundamental importance in understanding the functioning of the adrenal medulla is its embryonic origin. Neuroblasts migrating outward from the primitive axis of spinal cord segments develop mainly into the ganglia of the sympathetic system; but some of them are transformed into the adrenal medulla. Thus most of these neuroblasts become sympathetic neurones; a small remnant become secreting cells which, on being stimulated, discharge adrenaline. Likewise, nearly all sympathetic neurones, when they are stimulated, discharge at their endings a substance which, according to strong presumptive evidence, has been regarded as adrenaline (Rosenblueth[1], 1932). Since adrenaline is the characteristic constituent when extracts are made of the adrenal medullary cells and since sympathetic neurones are like the medullary cells in origin and in producing adrenaline, or an adrenaline-like substance, the question arose whether extracts of these neurones might not yield adrenaline.

The answer to that question was sought by Lissák and myself[2]

* Presented October 27, 1939 at The New York Academy of Medicine in the Twelfth Graduate Fortnight.

(1939). We found that extracts of the ultimate sympathetic fibers, the "adrenergic" fibers (e.g., those in the mesenteric nerves) or extracts of an organ containing such fibers (e.g., the heart) have all the effects of extracts of the adrenal medulla itself. They are like adrenaline in raising blood pressure, dilating the pupil, contracting the nictitating membrane, relaxing the non-pregnant cat uterus, augmenting the heart beat, and in other similar respects. Extracts of "cholinergic" nerves, and also extracts of the heart in which adrenergic fibers had degenerated, had no distinctive adrenaline-like action on blood pressure or iris.

The evidence strongly indicates, therefore, that Elliott's[3] (1904) suggestion is correct, that the ultimate sympathetic neurones influence glands and cardiac and smooth muscle by the adrenaline which they set free at their terminals, and that adrenaline secreted from the adrenal medulla and circulating in the blood stream has on these structures the same influence as the nerve impulses because it is the same substance as that which they produce. Since the sympathetic division of the autonomic system when strongly excited acts as a whole and thereby induces wide-spread changes in the organism—e.g., stopping the digestive processes, raising blood pressure, accelerating the heart, erecting hairs, as well as discharging adrenaline from the adrenal medulla—the combined, simultaneous action of sympathetic neuronal adrenaline and secreted medullary adrenaline is properly regarded as constituting a sympathico-adrenal system.

In addition to adrenaline discharged from the adrenal medulla, as a means of reinforcing or prolonging the effects of sympathetic nerve impulses, there is sympathin. This is a substance which escapes into the blood stream, from organs innervated by the sympathetic, when the sympathetic system is specially active. As we have noted, in these circumstances adrenaline is discharged from the nerve endings and has its typical effects. In doing so, however, some change occurs, because in some regions—in smooth muscles, for example—it causes relaxation and in others contraction. Rosenblueth and I[4] (1933), following a theory offered by Langley, have suggested that neuronal adrenaline unites inside the reacting cells with a differentiating substance which makes possible the two opposite responses to a single agent. In any case, sympathin differs from adrenaline. For example, ergotoxine blocks the hypertensive action of adrenaline on blood pressure and reveals a depressive action; it has not that influence on the action of sympathin.

And whereas adrenaline retracts the iris and relaxes the cat's non-pregnant uterus, sympathin does not do so if it comes from a region where sympathetic nerves have a purely positive influence. In general, however, the positively acting sympathin prevails, causing, for example, acceleration of the heart and rise of blood pressure. The observations which Rosenblueth and I[5] made in 1932, and which later were extended by Liu[6] (1935), proved that secreted adrenaline and circulating sympathin, liberated from stimulated structures, coöperate in augmenting or lengthening the duration of such changes. A brief period of excitement will discharge adrenaline from sympathetic nerve endings; sympathin will come away from the affected organs and also adrenaline from the adrenal medulla. These circulating sympathico-mimetic substances may have effects which outlast for minutes the exciting incident—effects which possibly explain the agitation which is experienced after the object or condition, which produced the excitement originally, has disappeared.

There was a time, about twenty years ago, when a lively controversy was going on between Stewart and Rogoff, then of Cleveland, and a group in the Harvard Physiological Laboratory as to whether the adrenal medulla responds to changes involving the sympathetic system by an extra discharge of adrenaline (Cannon,[7] 1929). The Cleveland investigators themselves furnished evidence that adrenal secretion is under control of the splanchnic nerves, for when they stimulated these nerves they saw a retraction of the denervated iris—a retraction which did not occur if the blood flow through the adrenal veins was obstructed during the stimulation, and which did occur when the pent blood was released. They denied the claims of the Harvard group, however, that afferent stimulation and asphyxia, which are accompanied by a natural discharge of splanchnic impulses, induce a similar increase of the secretion. In 1922, Carrasco-Formiguera and I,[8] using as an indicator the denervated heart instead of the denervated iris, provoked an acceleration of the heart rate by stimulating afferent nerves or inducing asphyxia. When we obstructed the blood flow through the adrenal veins these reflex and asphyxial effects did not occur, and when the pent blood was released the heart was again accelerated. The logic of the situation thus presented required Stewart and Rogoff to accept our evidence for reflex and asphyxial secretion from the adrenal medulla or to repudiate the evidence on which they based the conclusion that the output of

adrenaline is under splanchnic control. That dilemma has not been met in the past seventeen years.

In reports of the work done by Stewart and himself, Rogoff[9] (1935) has repeatedly and insistently laid stress on the fact that they employed a quantitative method. The method involved collecting blood from the adrenal veins as it gathered during a measured time in a section of the inferior vena cava, the so-called "cava pocket," and then assaying the adrenaline content of this blood by comparing its effect and that of various concentrations of adrenaline on a beating intestinal strip. By use of this method the Cleveland investigators obtained results which led them to infer that adrenal secretion is constant and unvarying; indeed, Rogoff has declared that the conclusion that asphyxia and central stimulation induce an extra output of adrenaline "has never been supported by satisfactory measurements of the rate of secretion." That statement indicates disregard for the results obtained by Rapport and myself[10] (1921), and by Sataké and his colleagues[11] (1927) with use of the very method which Stewart and Rogoff devised. For more than a dozen years the Japanese investigators labored in this field. They published a large volume of experimental studies which definitely and quantitatively confirmed the results obtained by the Harvard group and which also clearly explained Stewart-and-Rogoff's failure as being due to too deep anesthesia. Rogoff has not only not attended to this evidence contradictory to his views; he has not attended to the studies of various observers—in Europe, Africa, South America—who with different methods have supported consistently our conclusions. Indeed, in the past twenty years there has been no support whatever, from any quarter, for the claims of the Cleveland pair. I offer no apology for recalling this old controversy, because there still appear in text books and even in a fairly recent publication of the American Medical Association (Rogoff,[9] 1935) statements which lead readers to conclude that the issue is not fully settled and that there is still some question about extra adrenal secretion when the sympathetic system is active.

As I have intimated, in the course of this controversy the denervated heart was used as an indicator of increased adrenaline in the circulation. It is extremely sensitive, responding by a faster beat when the adrenaline concentration is increased by only 1 part in 1,400,000,000 parts of blood. When, with aseptic precautions, the heart has been isolated from the nervous system the animal may live indefinitely, with the heart con-

tinuing to perform its proper functions as a pump (Cannon, Lewis and Britton,[12] 1926). Hence, while the animal is in excellent physical condition, records can be made of the heart rate under various experimental conditions and thereafter the adrenal glands can be excluded from action—by removing one of them and denervating the other—and records of the heart rate then made again under the same conditions. Thus, by finding that an acceleration occurred during the tests, and that acceleration failed to occur after adrenal inactivation, we were able to show that muscular work, emotional excitement, asphyxia, low blood pressure, external cold, infection, and hypoglycemia were accompanied by an extra secretion from the adrenal medulla, and extra activity of the sympathico-adrenal system.[9,10,11,12] Each one of these situations makes a special demand on the organism or is likely to make that demand. In each one of them the operation of the system is such as to favor the welfare of the organism. The blood flow is shifted in such manner as to promote effectiveness in muscular effort, the metabolic rate is speeded up when the temperature tends to fall, glucose is liberated from hepatic stores when the amount in the blood is dropping to a low level, the capacity of the blood vessels is adapted to a reduced blood volume. In short, as these illustrations indicate, the system promptly and automatically makes adjustments which are required to prepare the organism for temporary exigencies or to preserve its normal internal condition when that is likely to be disturbed. Such services performed by the sympathico-adrenal system at times of unusual or critical need I have called its "emergency" functions (Cannon,[7] 1929).

Much of the evidence that the sympathico-adrenal system performs its special services in times of stress was gained by study of animals—dogs, cats, monkeys—from which that system had been wholly removed. The possibility of continued existence without any sympathetic nerves may seem surprising, for they belong to what have been called "Lebensnerven." Yet we have been able, quite easily, to keep sympathectomized animals under the quiet and uniform conditions of the laboratory many months—in one instance more than three years—in good health and nutritional status. Cats were most thoroughly investigated. So long as they were not subjected to stress they appeared quite normal. But when they were exposed to heat or cold they were revealed as defective in their ability to maintain body temperature; when they lost blood they were defective in restoring compensatory blood pressure; when they

ran or struggled the blood pressure fell and they fainted; when placed in an atmosphere of low oxygen concentration they collapsed much sooner than animals with the sympathico-adrenal system intact; and when given insulin in amounts readily endured by normal cats they suffered a sharp drop in blood-sugar percentage which would have been disastrous if they had not been rescued (Cannon,[13] 1939). It was interesting to learn that although sympathectomized dogs showed in emergencies effects similar to those shown by sympathectomized cats the effects were not so extreme. The difference can reasonably be ascribed to the remarkable physiological developments which the dog possesses as a running animal: a much larger lung surface, cardiac capacity and blood volume for his weight than the more indolent cat possesses, in addition to having a higher hemoglobin percentage, a readier resort to shivering when cold and resort to panting when warm. Note that in all these respects removal of the sympathico-adrenal system produces no adverse alteration. There is one condition in which these advantages of the dog cannot be effective—i.e., in the mobilization of sugar from the liver when an excess of insulin is given. In those circumstances the sympathectomized dog is as vulnerable as the sympathectomized cat (Cannon,[14] 1939). It appears, therefore, that the sympathico-adrenal system is called into action in emergencies and has a fundamentally important function in maintaining a fairly uniform condition in the fluid matrix of the organism, the blood and lymph (Cannon,[13] 1939).

The foregoing discussion has been concerned chiefly with the combined functions of the sympathetic division of the autonomic system and the secretion of the adrenal medulla—i.e., with the functions of the sympathico-adrenal system. The question arises as to whether secreted adrenaline, itself, has a distinctive use. Rogoff[9] (1935) has declared that it does not play an important role in the body and that "no specific function for epinephrine (adrenaline) has been proved." The main argument against the utility of secreted adrenaline is based on the fact that one adrenal may be removed and the other may be demedullated without endangering the life of the animal. Obviously the adrenal medulla is not essential to existence. There is a difference, however, between being useful and being essential. As we have many times demonstrated, the cardiac nerves may all be severed in animals which survive the operation for many months; the nerves are clearly not essential, but is there anyone who would suppose, therefore, that they are not useful? Simi-

larly the survival of animals without the sympathetic system proves that it is not essential, but again are we to conclude, therefore, that it is not useful? In order to know the utility of adrenaline we must consider what changes are wrought by exclusion of the adrenal medulla, quite apart from continued existence.

First, there is the coöperation between secreted adrenaline, neuronal adrenaline and circulating sympathin, already referred to. Actual records show, as previously noted, that a momentary excitement may have bodily effects lasting 15 to 20 minutes if the adrenals are present and only brief effects if the glands are excluded from action. These records prove that adrenaline intensifies and prolongs the influence of sympathetic impulses.

Again, adrenaline has an accelerating action on metabolism. One milligram of adrenaline will cause an increased output of heat amounting to 50 calories. I have already mentioned the evidence, derived from experiments on animals with the heart denervated, that when the body temperature tends to drop, because of exposure to external cold, there is an increased secretion from the adrenal medulla. If the adrenal influence is suppressed and the animals, thus rendered defective, are subjected to the same conditions as before, shivering occurs to a greater degree than when the adrenals were present and able to augment metabolism, i.e., the animals fall back on muscular contraction as a means of producing extra heat.

Another effect of adrenaline which has been reported by a number of investigators—among them Mendenhall and myself[15] (1914)—is that of hastening the coagulation of the blood. When adrenaline is injected this phenomenon occurs, and when adrenaline is secreted, either as a consequence of splanchnic stimulation or as a consequence of excitement, the time of coagulation is likewise greatly shortened. If the adrenal medulla is excluded and the conditions which normally evoke secretion are repeated, the faster clotting does not occur.

Finally, there is the special effect of adrenaline on the liver. In 1928 Riegele[16] described a network of extremely delicate nerve filaments between the liver cells, with offshoots reaching into the cellular cytoplasm. This observation, if correct, would establish a basis for immediate nervous government of liver function. The observation, however, has been questioned. Two years ago Nonidez[17] (1937) reported that the silver method used by Riegele not only may stain nerve fibers but

also may impregnate fine connective tissue strands and thus confuse the picture. "Up to the present," Nonidez wrote, "no nervous structure resembling a network has been described in the liver."

The testimony that nerve filaments are not distributed to liver cells is in accord with the evidence that a relatively small dose of insulin induces a swift and unchecked and quite abnormal fall of blood sugar in animals from which the adrenals have been removed, although hepatic nerves are still intact (Cannon, McIver and Bliss,[18] 1924). It is also in accord with observations that emotional excitement does not cause the usual hyperglycemia in animals without adrenals, but again with hepatic nerves intact (Britton,[19] 1928). Supporting evidence was furnished by the experiments which Lissák and I[2] (1939) performed this year. It will be recalled that we found an adrenaline-like substance in the ultimate sympathetic neurones, whether these neurones, or parts of them, were isolated or were imbedded in organs, e.g., the heart. The significant fact appeared, that whereas extracts of liver *blood vessels* raised blood pressure, dilated the pupil and speeded up the heart rate—thereby revealing the presence of sympathetic fibers on them—extracts of liver *pulp* had little or no adrenaline-like action. The occasional slight action can be explained as due to the difficulty of removing the pulp from the vessels without pulling away some of the vascular twigs. All these observations, taken together, indicate clearly that the liver cells are not subject to direct nervous control.

It appears that the liver can play a role in carbohydrate metabolism quite independently, both by taking in and giving forth glucose. By a simultaneous determination of the rate of blood flow through the liver and the glucose content of the inflowing and the outflowing blood it has been shown that during control periods the liver secretes glucose, and that when glucose is abundantly supplied secretion ceases and sugar is retained (Soskin, Essex, Herrick and Mann,[20] 1938). In an emergency, however, as, for example, in great excitement or when insulin is abundant, this intrinsic mechanism is not adequate. Faster glycogenolysis is required in order to mobilize blood sugar. In these circumstances, adrenaline discharged from the adrenal medulla is the effective agent for releasing glucose from the hepatic stores.

Because an injection of adrenaline raises blood pressure, by accelerating the heart and constricting arterioles, an idea has prevailed that persistent hypertension may result from overactivity of the adrenal

medulla. In a temporary test, as Freeman and Jeffers[21] (1939) have shown, secreted adrenaline may play a significant role in producing a brief experimental hypertension, but that occurred when the heart was denervated and when its acceleration depended on medulliadrenal secretion. If the heart was normally innervated, the effect was produced quite as well without any participation of the adrenal glands. Again we note a coöperation of adrenaline and sympathetic impulses in the sympathico-adrenal system—a coöperation which permits either of the partners to compensate, in this condition, for absence of the other. But neither of these partners is necessary for the maintenance of normal blood pressure. The entire sympathetic system may be progressively removed and yet vascular tone is well preserved and the pressure is held within the normal range (B. Cannon,[22] 1931). This is not a consequence of compensatory secretion of adrenaline, for there is experimental proof that the adrenal medulla does not secrete unless it is stimulated by nervous impulses, except in the rare state of extreme asphyxia (Zwemer and Newton,[23] 1928). The sustained contraction of the arterioles after sympathectomy appears to be due to intrinsic properties of the smooth muscle in the vessel walls.

Two types of prolonged hypertension can be produced experimentally: one the result of removal of the restraining nerves (i.e., those from the carotid sinus and the aortic arch), as demonstrated by Heymans and his collaborators; the other the result of lessening the blood flow through the kidneys, as demonstrated by Goldblatt and his collaborators (Cannon,[24] 1937). The former type, Heymans and Bouckaert[25] (1936) report, disappears when the sympathico-adrenal system is entirely excluded from action. Whether this type ever occurs clinically is as yet unknown. The second type—that produced by Goldblatt clips on the renal arteries—is not affected by sympathectomy. Freeman and Page[26] (1937) have found that application of the clips induced hypertension in completely sympathectomized animals and that if hypertension had been produced by partial renal ischemia, later removal of the sympathetic did not improve the condition. I have felt justified in emphasizing the absence of evidence that excessive adrenal secretion explains high blood pressure because, unfortunately, the idea that the adrenals are the cause of it has prevailed and has led to severe operations directed towards denervating them in order to abolish their supposedly pernicious discharge. There is no doubt that if adrenal secre-

tion should be discharged in sufficient amount to produce a high blood pressure it would have other wide-spread and highly disturbing effects on the organism such as are, in fact, not seen in cases of hypertension.

In summarizing the part played by the adrenal medulla in the functioning of the organism we may recognize that it coöperates with sympathetic impulses in producing adrenaline, that this sympathico-adrenal system is brought prominently and usefully into action in emotional excitement, in vigorous muscular work, in asphyxia, low blood pressure, chilling surroundings and hypoglycemia—in brief, that it serves effectively in emergencies; furthermore, that this service can be given a general expression in stating that the system guards the constancy of the internal environment of the organism; and finally that secreted adrenaline itself acts to prolong the effects of nerve impulses, to accelerate metabolism, to shorten coagulation time and to release glucose from the liver. There is no evidence that secreted adrenaline is an important agent in maintaining a high blood pressure.

REFERENCES

1. Rosenblueth, A. The chemical mediation of autonomic nervous impulses as evidenced by summation of responses, *Am. J. Physiol.*, 1932, *102:* 12.
2. Cannon, W. B. and Lissák, K. Evidence for adrenaline in adrenergic neurones, *Am. J. Physiol.*, 1939, *125:* 765.
3. Elliott, T. R. On the action of adrenalin, *J. Physiol.*, 1904, *31:* xx.
4. Cannon, W. B. and Rosenblueth, A. Sympathin E and sympathin I, *Am. J. Physiol.*, 1933, *104:* 557.
5. Rosenblueth, A. and Cannon, W. B. Some effects of sympathin on the nictitating membrane, *Am. J. Physiol.*, 1932, *99:* 398.
6. Liu, A. C. The coöperative action of sympathetic nerve impulses, adrenine and sympathin on the nictitating membrane of the cat, *Am. J. Physiol.*, 1935, *112:* 690.
7. Cannon, W. B. *Bodily changes in pain, hunger, fear and rage.* New York, Appleton, 2. ed., 1929.
8. Cannon, W. B. and Carrasco-Formiguera, R. Further evidence for reflex and asphyxial secretion of adrenin, *Am. J. Physiol.*, 1922, *61:* 215.
9. Rogoff, J. M. The adrenal medulla, in: *Glandular physiology and therapy.* Chicago, A.M.A., 1935, p. 279.
10. Cannon, W. B. and Rapport, D. Further observations on the denervated heart in relation to adrenal secretion, *Am. J. Physiol.*, 1921-22, *58:* 308.
11. Sataké, Y., Sugawara, T. and Watanabé, M. Method for collecting blood from suprarenal gland in the dog, *Tohoku J. Exper. Med.*, 1927, *8:* 501; and Effect of fastening and of sensory stimulation upon the rate of epinephrine output from the suprarenal gland in dogs, *ibid.*, 1927, *9:* 1.
12. Cannon, W. B., Lewis, J. T. and Britton, S. W. Lasting preparation of the denervated heart for detecting internal secretion with evidence for accessory accelerator fibers from the thoracic sympathetic chain, *Am. J. Physiol.*, 1926, *77:* 326.
13. Cannon, W. B. *The wisdom of the body.* New York, Norton, Rev. ed., 1939.
14. Cannon, W. B. Some new aspects of homeostasis (William Henry Welch lecture), *J. Mt. Sinai Hosp.*, 1939, *5:* 587.
15. Cannon, W. B. and Mendenhall, W. L.

The hastening of coagulation by stimulating the splanchnic nerves, *Am. J. Physiol.*, 1914, *34:* 243.

16. Riegele, L. Über das feinere Verhalten der Nerven in der Leber von Mensch und Säugetier, *Ztschr. f. mikr.-anat. Forsch.*, 1928, *14:* 73.
17. Nonidez, J. F. Nervous terminal reticulum. Critique; observations on the thyroid and the liver, *Anat. Anz.*, 1937, *84:* 1.
18. Cannon, W. B., McIver, M. A. and Bliss, S. W. A sympathetic and adrenal mechanism for mobilizing sugar in hypoglycemia, *Am. J. Physiol.*, 1924, *69:* 46.
19. Britton, S. W. The prepotency of medulliadrenal influence in emotional hyperglycemia, *Am. J. Physiol.*, 1928, *86:* 340.
20. Soskin, S., Essex, H. E., Herrick, J. F. and Mann, F. C. The mechanism of regulation of the blood sugar by the liver, *Am. J. Physiol.*, 1938, *124:* 558.
21. Freeman, N. E. and Jeffers, W. A. Effect of progressive sympathectomy on hypertension produced by increased intracranial pressure, *Am. J. Physiol.*, 1939, *126:* P493.
22. Cannon, B. The effects of progressive sympathectomy on blood pressure, *Am. J. Physiol.*, 1931, *97:* 592.
23. Zwemer, B. L. and Newton, H. F. Asphyxial stimulation of the denervated adrenal gland, *Am. J. Physiol.*, 1928, *85:* 507.
24. Cannon, W. B. Factors affecting vascular tone (George E. Brown memorial lecture), *Am. Heart J.*, 1937, *14:* 383.
25. Heymans, C. and Bouckaert, J. J. Hypertension artérielle chronique expérimentale et sympathectomie, *Bull. Acad. roy. de méd. de Belgique,* 1936, *1:* 42.
26. Freeman, N. E. and Page, I. Hypertension produced by constriction of renal artery in sympathectomized dogs, *Am. Heart J.*, 1937, *14:* 405.